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Pestalozzi, B C

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Breast cancer metastases to the central nervous system (CNS) include the clinically distinct situations of multiple brain metastases (78%), solitary brain metastasis (14%), and leptomeningeal metastases (8%) [1, 2]. CNS metastases occur in 10%–16% of stage IV patients while they are found in ~30% of patients in autopsy series [1]. In populations of early breast cancer patients treated on adjuvant trials, CNS-recurrence rates of 3%–6% have been observed [3, 4]. CNS recurrences have consistently been found to occur with increased frequency in younger and premenopausal patients as well as in estrogen receptor (ER)-negative and/or progesterone receptor (PgR)-negative cancers. While some series found correlations of CNS recurrences with nodal status, high tumor grade, tumor size, and HER2 status [4], other series have described associations with high S phase, aneuploidy, and p53 positivity [3]. There was no correlation between CNS recurrences and type of adjuvant systemic treatments [3, 5]. Several groups have reported an increased frequency of CNS recurrence in patients with lung metastases [4, 6].

In the April issue of *Annals of Oncology*, a series of 679 'triple receptor-negative' (ER negative, PgR negative, and HER2 negative) early breast cancer patients treated at the M. D. Anderson Cancer Center in Houston from 1980 to 2006 are described, in which 42 (6.2%) developed brain metastases after a median follow-up of 26.9 months [7]. Similar findings were reported at the 2008 American Society of Clinical Oncology meeting from Wiesbaden, Germany. Of the 338 patients with triple receptor-negative breast cancer treated from 1989 to 2006, cerebral metastases developed in 19 (5.6%) [8]. In the German study, triple receptor-negative breast cancer brain metastases developed earlier than in other receptor subtypes, occurring at a median interval of 22 months after primary diagnosis versus 51 months for all other subtypes. In addition, both groups have reported that overall survival of patients with triple receptor-negative tumors who develop CNS metastases is particularly dismal, with median survival times of 2.9 and 4 months, respectively [7, 8].

How can we put these findings into context, what is new about them? And what are the possible implications of these findings, for clinical management and for research?

Currently, clinical and translational research in breast cancer concentrates on dissecting the heterogeneity of the disease into different subtypes. Gene expression profiles classify breast cancers into luminal, basal and HER2-positive subtypes with clearly different prognostic significance [9]. Clinical scientists and pathologists have approximated these molecularly defined categories by using expression of ERs and PgRs as well as expression and/or amplification of HER2 which are readily available predictive factors [10, 11]. In this approximation, the new category of triple receptor-negative breast cancer has been created which comprises ~15% of all breast cancers and ~85% of basal-type tumors. Nevertheless, the category of triple-negative breast cancer is by no means a homogeneous group, and even when using additional 'basal' markers such as CK5/6, EGFR, P-cadherin, and/or lymphocyte infiltration, overlap with basal-like tumors remains incomplete [12]. Additional molecular features characterizing smaller subgroups of triple-negative cancers are p53 mutations, BRCA1 mutations, and others. Obviously, all these associations deserve and need additional investigation. For the time being, a word of caution seems appropriate; while 'triple negative' is a handy designation for clinicians, it is an unsatisfactory category in at least three ways: it is not a biologically homogeneous subgroup, it does not help to select a particular treatment (it only allows to avoid endocrine and HER2-directed treatments), and its prognosis overall is worse. While a subset of patients with triple-negative breast cancer can be cured with the addition of adjuvant chemotherapy, others relapse quickly despite such treatment [13]. It is not uncommon that patients who hear of their triple-negative cancer and particularly those who read about it on the Internet return to their oncologist with 'triple unhappiness'. We have previously known that ER-negative and PgR-negative breast cancers are more likely to develop CNS metastases [3, 4]. Now, we have learned that in triple-negative breast cancer they appear particularly early and have a particularly dismal prognosis [7, 8].

There is considerably more information available about CNS metastases in HER2-positive disease which should be included into this discussion. Recently, the M. D. Anderson group has published a large retrospective analysis of breast cancer patients with CNS metastases and known HER2 status [14]. A total of 598 patients from 1994 to 2006 were included, and 280 HER2-positive patients were compared with 318 HER2-negative patients. Time to brain metastasis and especially time from brain metastasis to death were longer for trastuzumab-treated HER2-positive disease (11.6 months) when compared with either HER2-positive disease not treated with trastuzumab (6.1 months) or HER2-negative disease (6.3 months).

Several other publications have reported high rates of CNS recurrences in HER2-positive breast cancer patients treated with trastuzumab [15–17]. Typically, CNS metastases become manifest, while systemic metastases are still responding to trastuzumab-containing regimens. This type of mixed response

is commonly attributed to the fact that trastuzumab is not able to cross the blood–brain barrier and appear in the cerebrospinal fluid [18]. Very recently, it has been reported that trastuzumab can penetrate into breast cancer CNS metastases as measured by PET scanning [19]. In contrast to the mAb trastuzumab (with a molecular mass of 145 kDa), the anti-HER2 and anti-HER1 small-molecule tyrosine kinase inhibitor lapatinib (581 Da) is able to cross the intact blood–brain barrier. Lapatinib has been shown to have some clinical activity in the treatment of brain metastases from HER2-positive disease [20] and to reduce the likelihood of CNS metastases in a large randomized study in advanced disease comparing capecitabine with or without lapatinib [21]. These and many other studies have generated a lot of enthusiasm because here is evidence that treatment decisions for metastatic disease should consider the site of metastasis. Nevertheless, the optimal approach remains uncertain in the case of a patient with HER2-positive disease who develops multiple CNS metastases while responding systemically to a trastuzumab-containing regimen. Should such a patient receive whole brain radiotherapy (WBRT) and continue systemic treatment including trastuzumab (leaving the possibility of future use of lapatinib for a second CNS progression), or should the patient receive WBRT and be switched to the lapatinib–capecitabine combination immediately [22]? Based on reports of increased survival after CNS metastases in HER2-positive patients treated with trastuzumab, the first option continues to be a reasonable choice [14, 23].

CNS metastases constitute a difficult clinical problem and are feared by patients and clinicians alike. They are usually accompanied by neurological deficits and are considered to be the main cause of death in more than half of the patients [5]. Treatment options include steroids (dexamethasone), surgical excision of solitary metastases, stereotactic radiosurgery for small (<3 cm) lesions not amenable to surgery, and WBRT. While the optimal combination of these options has clearly improved the prognosis, the median survival time of patients with CNS metastases is 4–6 months, and only 20%–40% of patients are alive at 1 year [5, 14]. New approaches are desperately needed. One possibility would be prophylactic cranial irradiation (PCI) as is routinely used for small-cell lung cancer. Would it be possible to define a subgroup of patients with a very high risk of CNS relapse who could potentially benefit from PCI? Unfortunately, the only data available do not support this approach. A series of 155 patients with metastatic disease screened for occult CNS involvement found 23 (14.8%) patients with occult disease [24]. Although the prognosis for these patients was reduced compared with those without occult CNS disease, there was no evidence that earlier treatment of CNS disease was beneficial. In 2006, the NCI launched an early CNS metastasis detection trial comparing 4-monthly to 12-monthly MRIs in HER2-positive stage IV breast cancer patients. Other trials are investigating temozolamide, lapatinib, and other approaches to prevent brain metastases. These trials are conveniently listed at www.BrainMetsBC.org. It is our duty to intensify research in this area. One aspect involving many clinical researchers around the world is the subproject investigations of CNS recurrences in the large adjuvant trials for HER2-positive disease such as the HERA trial and the ALTTO trial. For the first time, these projects analyze in adequate detail the type of CNS recurrence and their relationship to systemic disease and to various treatments including trastuzumab and lapatinib. Similarly, all the randomized adjuvant trials conducted in HER2-positive disease with trastuzumab and/or lapatinib should have rigorous and special documentation of CNS recurrences.

At the same time, research of brain metastases in animal models has gained considerable momentum. Starting with human breast cancer cells harvested from a pleural effusion and injecting them into the left cardiac ventricle of nude mice, harvesting brain metastases and reinjecting them again into nude mice, it has been possible to establish mouse model systems of brain metastases [25]. Using these models, mechanistic studies of the roles of angiogenesis, energy metabolism, HER2 and Stat3 signaling pathways, as well as of metastasis dormancy are being carried out. For example, a brain tropic subline of the human MDA-MB-231 breast cancer cell line (231BR) was transfected with low or high amounts of HER2. Compared with the parental line, the HER2 transfectants yielded threefold greater numbers of large brain metastases [26]. This result shows that the high incidence of brain metastases in HER2-positive disease probably has a biologic basis and is not only due to the pharmacokinetic fact that trastuzumab cannot penetrate the intact blood–brain barrier.

Investigations into the molecular basis of metastasis to bone and lung in breast cancer have been very successful [27]. Genes used for initiation, progression, and virulence of metastasis and genes for interactions between tumor cells and their stroma have been described [28]. The seed and soil hypothesis has been developed into a conceptual framework for testing the cellular processes involved in metastatic progression. Joan Massagué's laboratory at Memorial Sloan Kettering has found that a lung-metastasis signature (but not a bone-metastasis signature) shows significant overlap with the brain-metastasis signature [29]. The hypothesis is that breast cancer cells invade the brain through functions provided by lung extravasation genes (plus functions provided by unique blood–brain barrier extravasation genes). This research finding corresponds well with the clinical observation that patients with lung metastases have an increased risk for the development of brain metastases. It is encouraging to note that progress in basic science is linking with clinical investigation.

B. C. Pestalozzi
Department of Oncology, University Hospital, Zurich, Switzerland
(E-mail: bernhard.pestalozzi@usz.ch)

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